REMARKS/ARGUMENTS

In response to the Office Action of June 14, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 39, 40, 42 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on September 22, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer markers of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation

error was corrected at page 1, line 23.

The "Description of the Figures" section has been amended to add sequence identification numbers and to clearly indicate that Figures 2 and 4 show the mass spectrum profiles of the disclosed biopolymer markers.

Several protocols at pages 41-45 have been amended to properly identify trademark names (TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 8 and 22), page 42 (line 14) and page 43 (lines 5 and 18) were underlined in the original disclosure and do not indicate text amended herein.

The paragraph at page 46 was amended to correct grammatical errors.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 12 in order to provide additional support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. Kits for determining the presence of the claimed biopolymer markers are discussed at page 47, line 10 to page 48, line 19; cerebrospinal fluid is noted to be one type of sample which can be used in the discussed kits. A typographical error within the same paragraph at page 49 has also been amended (skill replaced skilled).

No new matter has been added by the amendments to the claims

made herein.

Claim 39 has been amended to remove the phrase "analysis of" from step (b) as it does not appear to add meaning to the claim as currently recited. Claim 39 has also been amended at step (c) to recite Markush language in the proper format.

Claim 40 has been amended to provide proper antecedent basis for the term "sample" in parent claim 39.

Claim 42 has been amended to correct an inadvertent omission of terms. Claim 42 as originally presented on September 22, 2003 recited a Markush grouping of mass spectrometric techniques, including Surface Enhanced Laser Desorption Ionization (SELDI) mass spectrometry (MS), Maldi Qq TOF, MS/MS, TOF-TOF, ESI-Q-TOF and ION-TRAP.

Claim 44 was amended to clearly indicate that the claimed kit is intended for use as a diagnostic tool, particularly for insulin resistance. The claimed peptides are identified as related to insulin resistance at page 46, lines 6-14. Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 10 to page 48, line 19.

Claims 45 and 46 were amended to provide proper antecedent basis for the term "kit" in parent claim 44.

Request for Rejoining of Claims

Claims 39-46 remain withdrawn from consideration on the merits at this time.

Considering that claims 39-46 are limited to the use of the peptides of claim 1 (amino acid residues 2-11 of SEQ ID NO:1, amino acid residues 2-12 of SEQ ID NO:2 and amino acid residues 2-13 of SEQ ID NO:3) a search of these claims would encompass these specific peptides. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptides of claim 1 are found to be novel, methods and kits limited to their use should also be found novel.

Oath/Declaration

Although the original declaration, filed on February 19, 2002, contains the signature of Dr. John Marshall (inventor 2), the date

of signature was omitted.

Applicants are in the process of preparing a new declaration and will forward this declaration to the Examiner as soon as it is completed and properly executed.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on January 13, 2005, remains rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in a such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner asserts that the instant invention still suffers insufficiency which would not enable one of ordinary skill in the art to use this invention without undue experimentation. The identified SEQ ID NOS are markers for diagnostic purposes. Applicant indicates that the mass spectral profiles of the digested peptides (SEQ ID NOS:1-3) are indications of the insulin resistance disease. However, the Examiner asserts that in view of the mass spectral profiles of the peptides as in Figures 2 and 4, there is not explanation or illustration what is the significance or relationship between these peptide fragments and insulin

resistance. Figure 2 is merely a trypsin digested spectra graph depicting ion 1208, whereas Figure 4 is a trypsin digested spectrum graph depicting ion 1447. There is no indication which graph represents insulin resistance patients. There is no indication where are the SEQ ID NOS fragments or the corresponding relationship to insulin resistance. The Examiner further asserts there lacks a scientific nexus between the mass spectrum of the recited SEQ ID NOS:1-3 and the target disease.

Applicants respectfully disagree with the Examiner's interpretation of the claimed invention.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

The disclosed method improves the efficiency of mass spectrometry by employing a combination of preparatory steps, e.g. chromatography and 1-D tricine polyacrylamide gel electrophoresis, to increase the amount of biopolymers that can be identified (see the instant specification as originally filed at page 25, line 9 to page 26, line 6). In the disclosed method, proteins (as separated on a tricine gel as shown in Figure 3) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and

identification (see, for example, page 38, lines 9-13 of the instant specification as originally filed). Identification of the differentially expressed peptides is accomplished by comparing the peptide mass and fragmentation pattern (mass spectral profile, for example, Figure 4) of the peptides with the peptide mass and fragmentation patterns of known peptides (page 40, lines 2-8).

For example, the gel photographed in Figure 3 shows a comparison of the protein content of samples obtained from patients having a history of insulin resistance or Type I diabetes with the protein content of samples obtained from patients determined to be normal with regard to insulin resistance and diabetes. Band #6, as shown in lane 4 of Figure 3, was resolved from a sample obtained from a patient with a history of insulin resistance and was identified as differentially expressed between a disease state (insulin resistance) and a non-disease state (normal). Subsequently Band #6 was excised from the gel and subjected to mass spectrometry (TOF MS/MS; Figure 4). The resulting mass spectral profile (sequence) was compared with a database of the sequences of known peptides and was identified as a fragment of the adrenergic alpha 2A receptor protein. The identified adrenergic alpha 2A receptor protein fragment weighs about 1447 daltons and is labeled as SEQ ID NO:3 at page 46, lines 6-14. Considering that the adrenergic alpha 2A receptor protein fragment (SEQ ID NO:3) was identified by

differential expression between insulin resistance and normal it is indicated as a potential disease marker for insulin resistance. The mass spectral profile of SEQ ID NO:3 as shown in Figure 4, as established by the instant invention, can be used as a reference for comparison with test samples. Accordingly, the presence of the mass spectral profile of SEQ ID NO:3 in a sample can potentially identify insulin resistance in the patient from which the sample was obtained, i.e. Figure 4 represents insulin resistance patients.

Thus, contrary to the Examiner's assertions, the instant specification does explain and illustrate the relationship between the claimed peptide fragments and insulin resistance.

Furthermore, Applicants respectfully submit that mass spectrometry is commonly practiced and one of skill in the art would know how to both carry out mass spectrometry protocols and how to analyze and obtain information from mass spectrometry profiles, i.e. one of skill in the art would know that, in order to identify a test peptide, the mass spectral profile of the test peptide is compared to the mass spectral profiles of peptides of known and/or predicted identity.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar

Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 1). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

As was previously noted above, in the disclosed method, proteins (as separated on a tricine gel as shown in Figure 3) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 9-13 of the instant specification as originally filed). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the

methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when

interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

In conclusion, Applicants respectfully submit that the instant specification, as originally filed, provides a clear explanation of the relationship between the recited peptides (SEQ ID NOS:1-3)

and insulin resistance. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification, and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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